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Reply to "The problem of the most appropriate curative treatment for hepatocellular carcinoma. When to embolize? When to operate?"

To the Editor:

We appreciate the valuable comments by Guerra *et al.* on our recently published article [1]. They raised some issues.

We recognize that surgical resection should be considered first, provided that patients are clinically eligible for this approach when considering liver function, portal pressure, remnant liver volume after surgical resection, and performance status. Vitale *et al.* [2] indicated that surgical resection can prolong survival compared with loco-regional therapy in patients with hepatocellular carcinoma (HCC), regardless of the Barcelona Clinic Liver Cancer (BCLC) stage, provided that liver dysfunction (Child-Pugh Class B or Model for End-stage Liver Disease score >9) and poor performance status (Eastern Cooperative Oncology Group >1) are absent. Indeed, it is more important to identify optimal candidates who will benefit from multi-disciplinary approaches rather than offering a formulaic treatment modality. Accordingly, nonsurgical approaches can also be considered in a patient with early stage HCC to avoid the risk of postoperative complications, including hepatic insufficiency and mortality, particularly for those with a morphologically cirrhotic liver on a preoperative radiological assessment. In this clinical setting, orthotopic liver transplantation (OLT) is a better option than surgical resection as it manages the underlying cirrhotic liver and HCC simultaneously. However, OLT is often ineligible due to the shortage of appropriate donors in South Korea.

Approximately, one-third of our study participants had a tumor burden within the Milan criteria [3], i.e., BCLC early stage, in which surgical resection or OLT may be recommended according to the degree of underlying liver disease. Surgical resection should be performed with caution in highly selected patients with BCLC early stage HCC and a morphologically cirrhotic liver, if they do not receive a suitable graft quickly. Furthermore, although patients who show BCLC early stage HCC and morphologically non-cirrhotic liver may be obviously good candidates for surgical resection, nonsurgical approaches can be considered in clinical practices for several reasons, such as patient refusal to undergo surgical resection, old age, relatively poor performance status, accompanying co-morbidities, evidence of portal hypertension, high indocyanine green retention test at 15 min, high liver stiffness value assessed using transient elastography [4,5], and inappropriate location for surgical resection based on the remnant liver volume.

The major aim of our study was to assess the impact of achieving a complete response (CR) at an early time point among patients with HCC treated with transarterial chemoembolization (TACE), not to compare the clinical outcomes between treatment modalities. When we stratified the 298 patients without tumor invasion of the peripheral portal vein branches into three groups; patients within the Milan criteria [3], patients beyond the Milan criteria, but within the up-to-seven criteria [6], and patients beyond the up-to-seven criteria, the patients within the Milan criteria had the highest CR rate (initial response, 82.9%), followed by those beyond the Milan criteria, but within the up-to-seven criteria (59.2%) (p <0.001 *vs.* those within the Milan criteria), and those beyond the up-to-seven criteria (13.7%) (p <0.001 *vs.* those beyond the Milan criteria, but within the up-to-seven criteria). Similarly, in the view of achieving a CR as the best response, patients within the Milan Criteria had the highest CR rate of 88.6%, followed by those beyond the Milan criteria, but within the up-to-seven criteria with 74.5% (p = 0.009 *vs.* those within the Milan criteria) and those beyond the up-to-seven criteria with 40.0% (p <0.001 *vs.* those beyond the Milan, but within the up-to-seven criteria) (Table 1). We agree that better clinical outcomes are anticipated after TACE in patients with a smaller tumor burden, but the prognostic significance of achieving a CR as the initial and best response was also observed in all three subgroups. Patients who achieved a CR (both initial and best response) had a longer median overall survival than the others

in the subgroup within the Milan criteria (Log-rank test, p <0.05). Similar results were obtained in the subgroup beyond the Milan criteria but within the up-to-seven criteria and the subgroup beyond the up-to-seven criteria (Log-rank test, all p <0.05).

Taken together, although we demonstrated the clinical significance of the response to TACE at an early time point, further studies are required for extended applications of surgical resection in patients with BCLC B stage HCC as well as those with BCLC A stage HCC and Child-Pugh A class liver function, but a morphologically cirrhotic liver.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Reduced mortality due to phlebotomy in moderately iron-loaded *HFE* haemochromatosis? The need for clinical trials

To the Editor:

We read with interest the paper by Bardou-Jacquet and colleagues [1] examining mortality in *HFE*-associated hemochromatosis and the accompanying editorial [2]. Both the authors of the study and the writers of the editorial concluded that the observation that *HFE* p.C282Y homozygotes with a serum ferritin (SF) at diagnosis between the upper limit of normal (ULN) and 1000 μg/L have reduced mortality compared to the population at large is predominantly due to venesection therapy.

We are not convinced however, that this conclusion is supported by the data provided for the following reasons:

1. If normalization of SF resulted in reduced mortality then it would be expected that *HFE* p.C282Y homozygotes with normal SF at diagnosis would also have reduced mortality but this was not found to be the case.
2. There was no information about the amount of iron removed for 36% of subjects so there was likely to be a significant minority of individuals with SF between the ULN and 1000 μg/L who did not have normalization of SF.
3. The cohort had a follow-up mean duration of 8.3 ± 3.9 years. The average age at diagnosis was 45.2 ± 14.2 years. This means that it is likely that many subjects in the group with SF between the ULN and 1000 μg/L had a raised SF for many more years than they had a normalized SF. It is not at all clear how this balance would result in reduced mortality when this was not seen among those with normal SF at diagnosis. Of those who did have information about the amount of iron removed, there is no information about whether they continued venesection therapy in order to maintain a SF level <50 μg/L after a SF of <50 μg/L was achieved initially, or the extent to which follow-up data (number and volume of phlebotomies, clinical and biochemical indicators of tolerance and efficacy of venesection therapy) were available. Moreover, there is no information about a formal, standardized, consistent, cohort-wide protocol around advising participants to start, continue and potentially stop venesection therapy, which makes the claim that the results can be interpreted as "intention-to-treat" difficult to justify.

Reasons other than the benefit of normalization of SF that could explain the study findings include:

1. Having a mild excess of iron in the body reduces the risk of cardiovascular and extra-hepatic cancer. This is counter intuitive with data suggesting that iron is a pro-oxidant and therefore more likely to result in increased cancer incidence. In addition we found an increase in the incidence of breast and colorectal cancer in a large cohort of *HFE* p.C282Y homozygotes compared to a matched *HFE* wild-type control group, we did not, however, have sufficient data to examine the association of cancer occurrence with SF levels [3]. From the